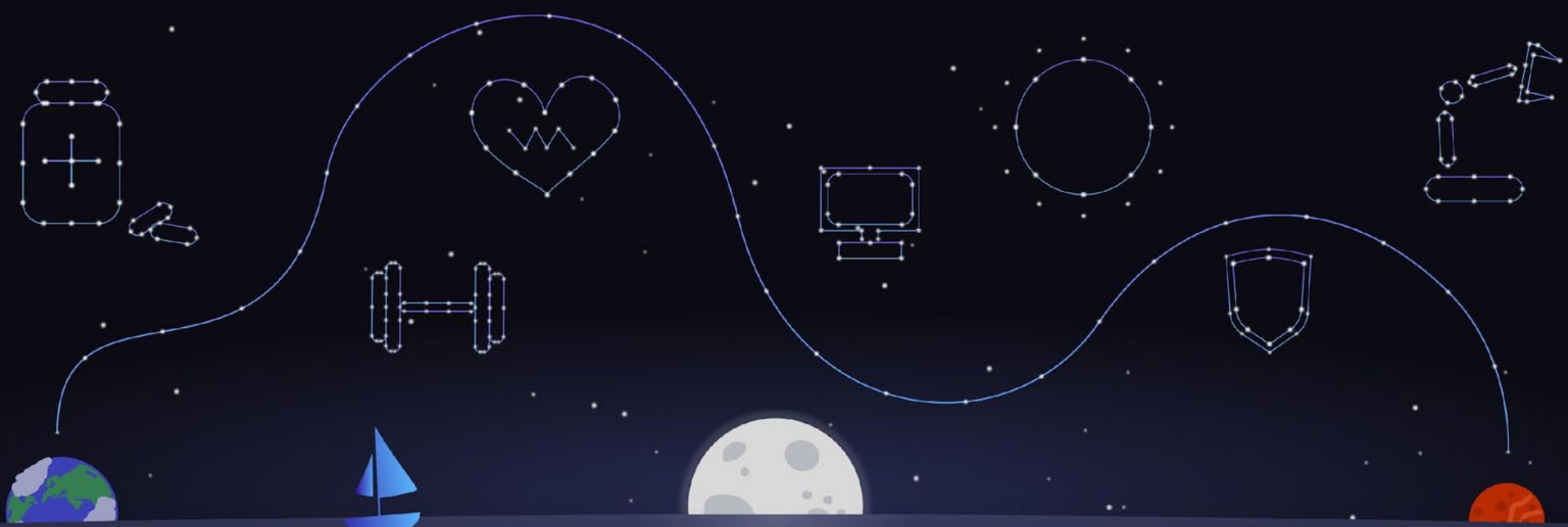

IMPROVING EFFICACY AND SAFETY OF PHARMACOLOGICAL TREATMENT THROUGH PRECISION HEALTH AND PHARMACOGENOMICS

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2022 NASA Human Research Program Investigators' Workshop

Pharmacogenomics background

PGx: what is it?

- Genetic variation in medication response (safety and efficacy)

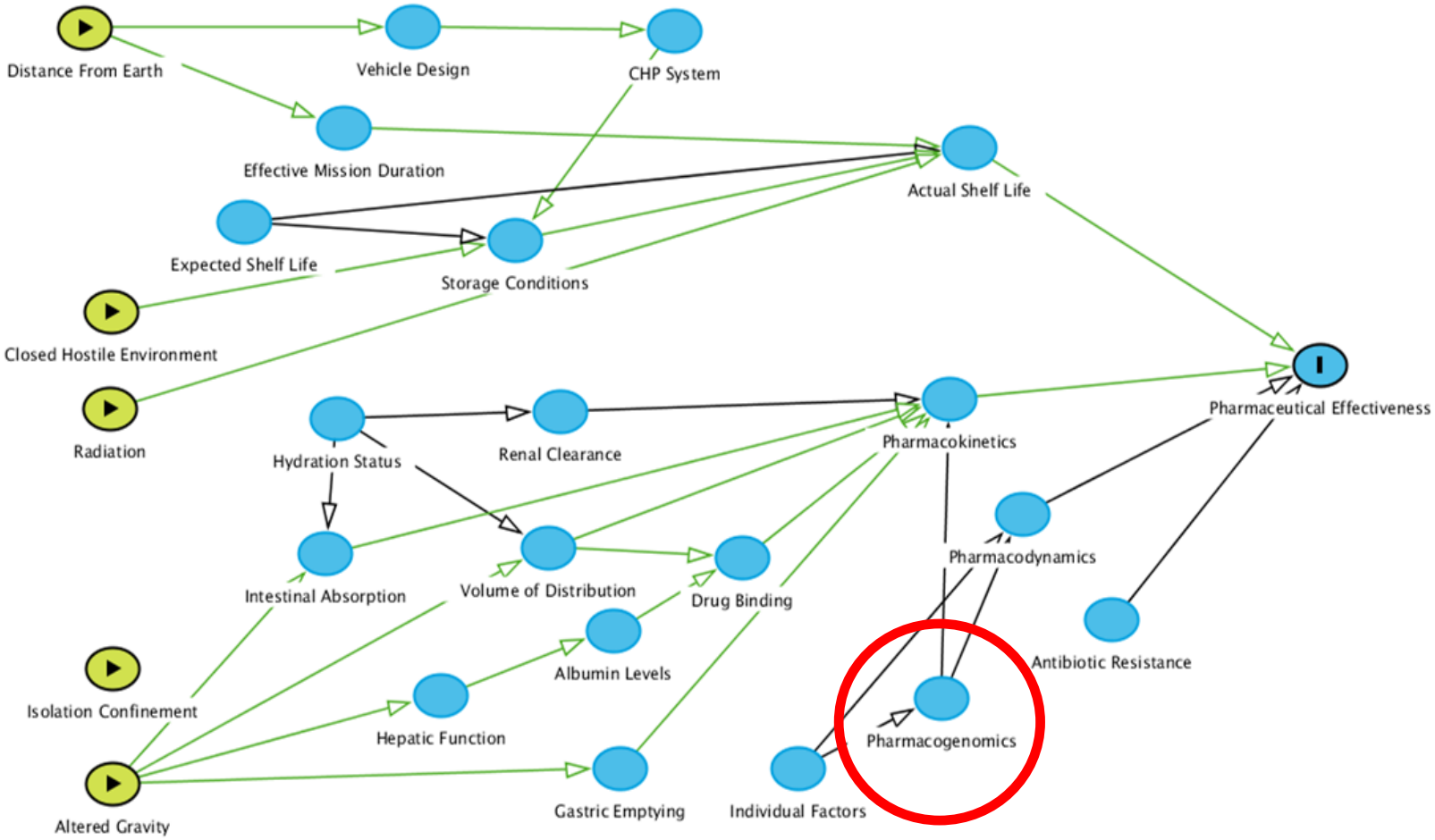
PGx: why do we need it?

- Limited mass and volume for spaceflight resupply, especially beyond LEO

PGx: what is currently available?

- Direct links to clinical therapeutic guidelines or recommendations

Pharmacogenomics background



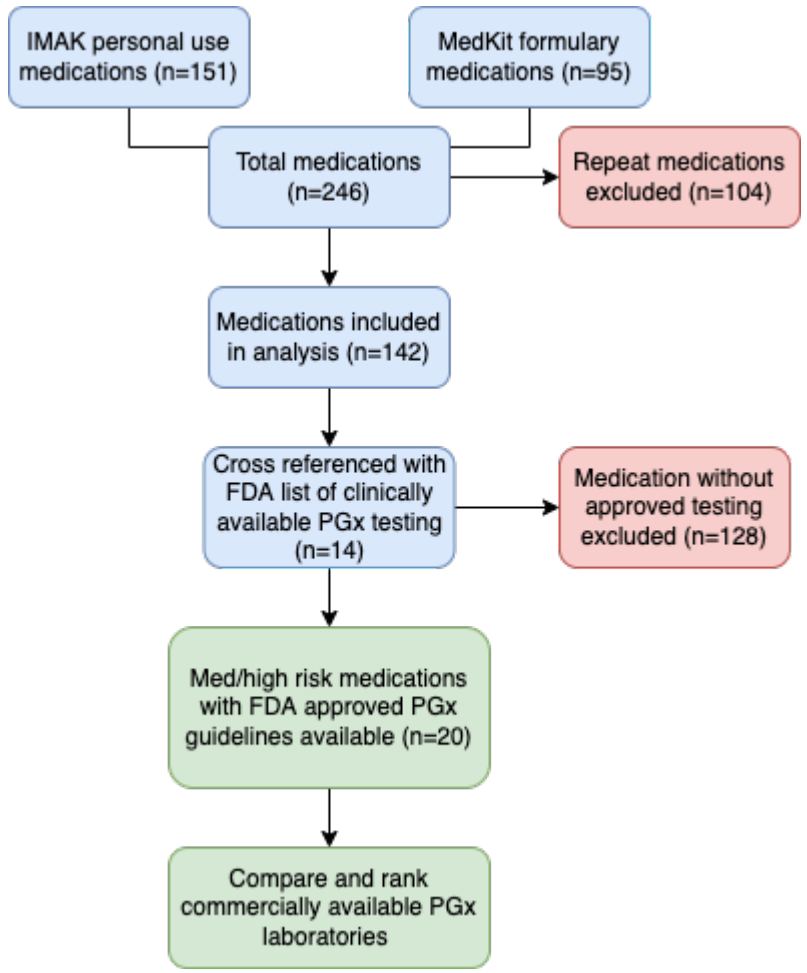
Methods

1. **ISS MedKit/IMAK data**

1. **Selection of candidate medications**

1. **Risk assessment via LxC table and workflow proposal**

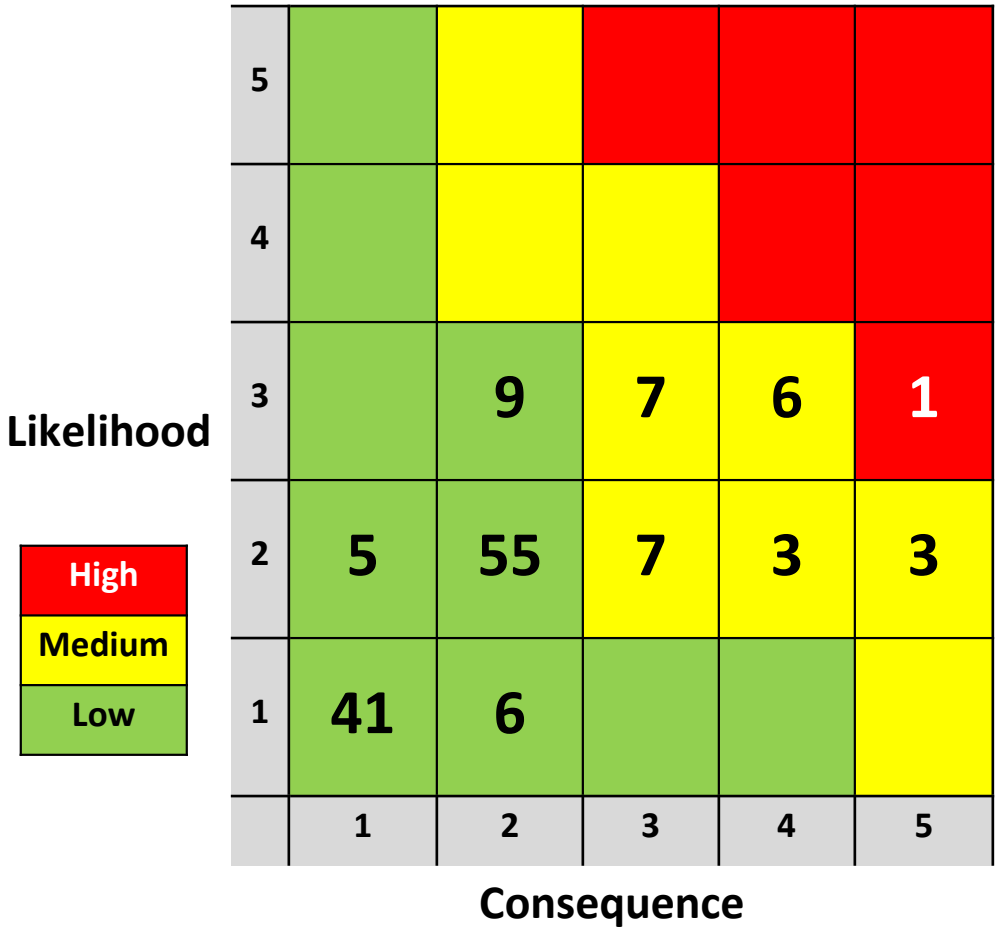
Flow chart showing drug/PGx selection process



Results

- **Likelihood**: 1-5 (very low to very high) event prevention
- **Consequence**: 1-5 (very low to very high) assessment criteria include safety, schedule, cost, technical

LxC 5x5 risk table for current ISS MedKit and IMAK medications showing risk of drug failure (as defined by composite of risk to safety and efficacy)



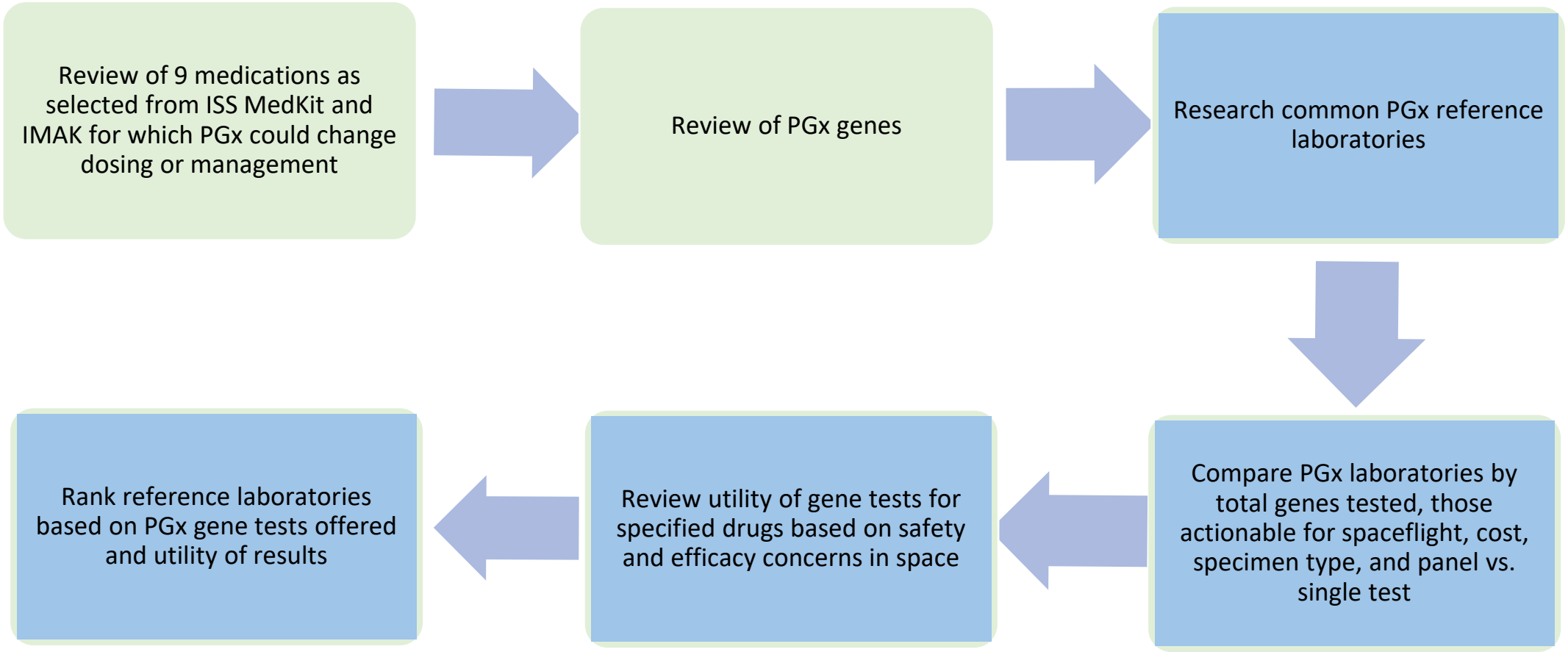
Results

10% of total medications in the ISS and IMAK have **FDA PGx impact**

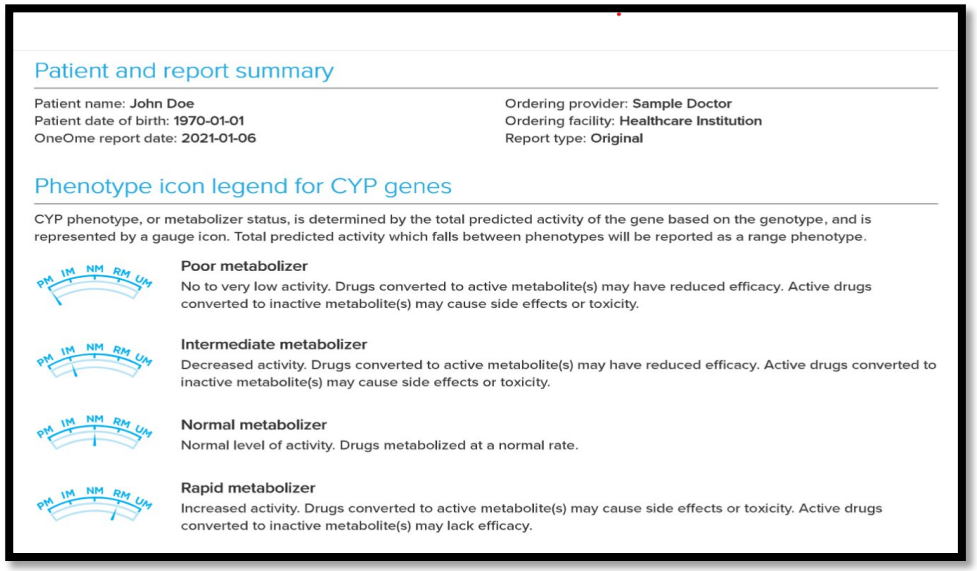
- Available PGx guidelines:
  - Anti-seizure medicines (phenytoin)
  - Non-steroidal anti-inflammatories (celecoxib)
  - Proton pump inhibitors (omeprazole)

Commercially available PGx testing

Methods


Review of 9 medications as selected from ISS MedKit and IMAK for which PGx could change dosing or management
Review of PGx genes
Research common PGx reference laboratories
Compare PGx laboratories by total genes tested, those actionable for spaceflight, cost, specimen type, and panel vs. single test
Review utility of gene tests for specified drugs based on safety and efficacy concerns in space
Rank reference laboratories based on PGx gene tests offered and utility of results

Results



Patient and report summary

Patient name: John Doe
Patient date of birth: 1970-01-01
OneOme report date: 2021-01-06

Ordering provider: Sample Doctor
Ordering facility: Healthcare Institution
Report type: Original

Phenotype icon legend for CYP genes

CYP phenotype, or metabolizer status, is determined by the total predicted activity of the gene based on the genotype, and is represented by a gauge icon. Total predicted activity which falls between phenotypes will be reported as a range phenotype.

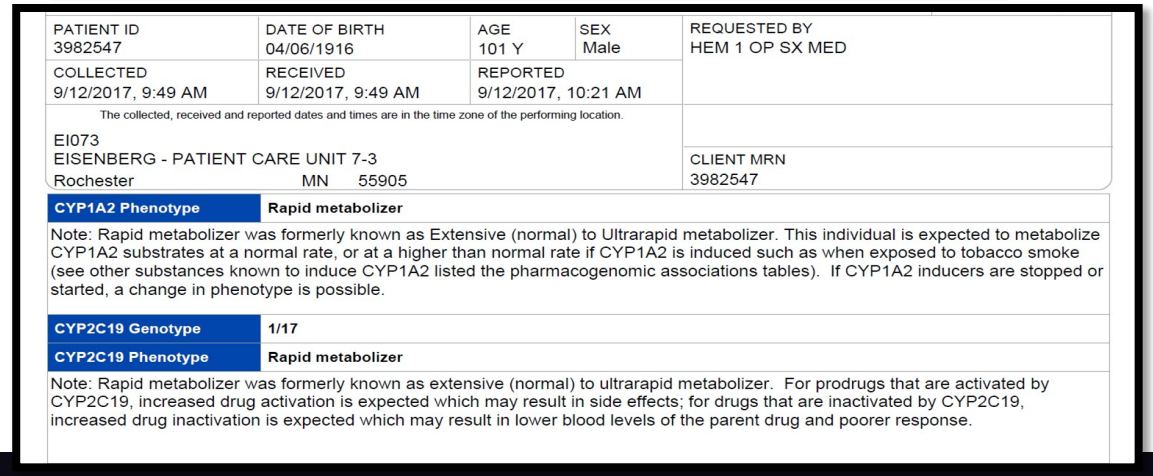
PM IM NM RM UM

Poor metabolizer
No to very low activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolite(s) may cause side effects or toxicity.

Intermediate metabolizer
Decreased activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolite(s) may cause side effects or toxicity.

Normal metabolizer
Normal level of activity. Drugs metabolized at a normal rate.

Rapid metabolizer
Increased activity. Drugs converted to active metabolite(s) may cause side effects or toxicity. Active drugs converted to inactive metabolite(s) may lack efficacy.



PATIENT ID	DATE OF BIRTH	AGE	SEX	REQUESTED BY
3982547	04/06/1916	101 Y	Male	HEM 1 OP SX MED
COLLECTED	RECEIVED	REPORTED		
9/12/2017, 9:49 AM	9/12/2017, 9:49 AM	9/12/2017, 10:21 AM		

The collected, received and reported dates and times are in the time zone of the performing location.

EI073
EISENBERG - PATIENT CARE UNIT 7-3
Rochester MN 55905

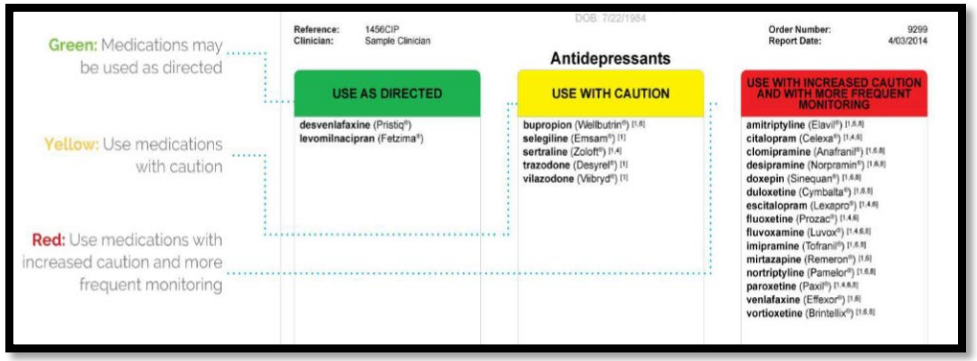
CLIENT MRN
3982547

CYP1A2 Phenotype	**Rapid metabolizer**

Note: Rapid metabolizer was formerly known as Extensive (normal) to Ultrarapid metabolizer. This individual is expected to metabolize CYP1A2 substrates at a normal rate, or at a higher than normal rate if CYP1A2 is induced such as when exposed to tobacco smoke (see other substances known to induce CYP1A2 listed the pharmacogenomic associations tables). If CYP1A2 inducers are stopped or started, a change in phenotype is possible.

CYP2C19 Genotype	**1/17**
CYP2C19 Phenotype	**Rapid metabolizer**

Note: Rapid metabolizer was formerly known as extensive (normal) to ultrarapid metabolizer. For prodrugs that are activated by CYP2C19, increased drug activation is expected which may result in side effects; for drugs that are inactivated by CYP2C19, increased drug inactivation is expected which may result in lower blood levels of the parent drug and poorer response.



Green: Medications may be used as directed

Yellow: Use medications with caution

Red: Use medications with increased caution and more frequent monitoring

Reference: 1456CIP
Clinician: Sample Clinician
Order Number: 9299
Report Date: 4/03/2014

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
desvenlafaxine (Pristiq®) levomilnacipran (Fetzima®)	bupropion (Wellbutrin®) selegiline (Emsam®) sertraline (Zoloft®) trazodone (Desyrel®) vilazodone (Viibryd®)	amitriptyline (Elavil®) citalopram (Celexa®) clomipramine (Anafranil®) desipramine (Norpramin®) doxepin (Sinequan®) duloxetine (Cymbalta®) escitalopram (Lexapro®) fluoxetine (Prozac®) fluvoxamine (Luvox®) imipramine (Tofranil®) mirtazapine (Remeron®) nortriptyline (Pamelor®) paroxetine (Paxil®) venlafaxine (Effexor®) vortioxetine (Brintellix®)

Common PGx reference laboratories by number of genes tested (total)

Common PGx Reference Laboratories	Number of genes tested total (number of genes actionable to spaceflight formulary)
Quest Diagnostics	44 (8)
RPRDx	38 (7)
Mayo Clinic	27 (7)
OneOme	27 (6)
Genelex	25 (6)
ARUP	18 (7)
Ariel Precision Medicine	11 (3)
MD Labs	9 (2)
Labcorp	5 (5)
GeneSight	N/A- MENTAL HEALTH
NeoGenomics	N/A- ONCOLOGY
Admera Health	N/A-TESTING SUSPENDED
Assurex	N/A- MENTAL HEALTH

Discussion

FDA PGx actionable drugs by gene and recommendations based on abnormal functioning[8]

Drugs	CYP Enzyme/Known genes	Recommendations based on FDA guidelines (except noted in red)
Naproxen	CYP2C9	No clinical recommendations
Diclofenac sodium gel	CYP2C8	No clinical recommendations
	CYP2C9	
Aspirin oral tablet	CYP2C9 (dose adjustments)	No clinical recommendations
	G6PD (risk of hemolysis)	Depends on the enzyme deficient, but no calculated exact increased risk reported, but do have higher risk of hemolytic episodes[1,9]
Hydrocodone and Acetaminophen (Vicodin HP)	CYP2D6 (dose adjustment)	No clinical recommendations
	COMT (dose adjustment)	No clinical recommendations
	OPRM1 (dose adjustment)	No clinical recommendations
Hydromorphone IM injection	OPRM1 (dose adjustment)	No clinical recommendations
	COMT (dose adjustment)	No clinical recommendations
Ibuprofen oral tablet	CYP2C8 (dose adjustment)	No clinical recommendations, controversy exists regarding the role of CYP2C8 and CYP2C9 polymorphisms in ibuprofen metabolism[3,8] No clinical recommendations
	CYP2C9 (dose adjustments)	No clinical recommendations
Omeprazole oral capsule	CYP2C19 (dose adjustments)	Dosing adjustments based on ultrarapid or poor metabolizer designations
Celecoxib (Celebrex) oral capsule	CYP2C9 (dose adjustments)	Poor metabolizers should receive half the lowest recommended dose
Phenytoin (Dilantin ER) oral capsule	CYP2C9 (dose adjustments)	Start at lowest dosing range and follow closely with frequent blood draws.
	HLA-B (drug induced hypersensitivity)	HLA-B*15:02 allele at high risk of Stevens-Johnson syndrome or toxic epidermal necrolysis (calculated risk of phenytoin-induced SJS/TEN is 0.65%) [6,7]

Discussion

PGx actionable drugs by gene and our top five reference laboratories

Drugs	CYP Enzyme/ known genes	Quest Diagnostics	ARUP Laboratories	Mayo Clinic Laboratories	RPRDx Diagnostics	OneOme
Aspirin oral tablet	G6PD	x	x	x	x	
	CYP2C9	x	x	x	x	x
Hydrocodone and Acetaminophen (Vicodin HP)	CYP2D6	x	x	x	x	x
	COMT	x		x	x	x
	OPRM1	x	x	x		x
Hydromorphone IM injection	OPRM1	x	x	x		x
	COMT	x		x	x	x
Ibuprofen oral tablet	CYP2C8	x	x		x	
	CYP2C9	x		x	x	x
Omeprazole oral capsule	CYP2C19	x	x	x	x	x
Naproxen sodium (Aleve) oral tablet	CYP2C9	x	x	x	x	x
Celecoxib (Celebrex) oral capsule	CYP2C9	x	x	x	x	x
Diclofenac sodium gel	CYP2C8	x	x		x	
	CYP2C9	x		x	x	x
Phenytoin (Dilantin ER) oral capsule	CYP2C9	x	x	x	x	x
	HLA-B	x	x	x	x	x
Cost		$900	Not available	Not available	Not available	Not available
Panel vs Single Test		Panel	Single tests	Single or Panel	Panel	Panel
Sample Types		Blood, saliva, buccal swab	Whole blood Alternative: saliva	Blood, saliva, buccal swab	Blood or saliva	Blood, buccal swab

Discussion

Proposed workflow for preflight PGx testing for ISS/IMAK precision health

Barriers and limitations

- Lack of PGx data interpretation training, provider uncertainty
- Despite PGx tailoring, further unknowns exist
- Disclosure and availability of information to astronauts

Benefits of PGx testing

- Reduce risk of adverse drug reactions and maximize drug efficacy
- Select medications terrestrially
- Preemptive sequencing
- Risk stratification and mitigation

Conclusion

- The field of pharmacogenomics (PGx) may have a role in the future of spaceflight
- Quest Diagnostics may be the most beneficial PGx reference laboratory for the current spaceflight formulary

Acknowledgements

- NASA Human Research Program
- HRP Precision Health Initiative Project
- JSC Aerospace Medical Clerk Program

References

1. Colonna P. Aspirin and glucose-6-phosphate dehydrogenase deficiency. Br Med J (Clin Res Ed). 1981; 283(6300):1189
2. . Daily EB, Aquilante CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. Pharmacogenomics. 2009; 10(9):1489–510
3. Dean L, Kane M. Phenytoin Therapy and HLA-B*15:02 and CYP2C9 Genotype: Medical Genetics Summaries. Bethesda, MD: National Center for Biotechnology Information; 2016.
4. Karnes JH, Rettie AE, Somogyi AA, Huddart R, Fohner AE, Formea CM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. Clin Pharmacol Ther. 2021; 109(2):302–9
5. Kathuria A, Moom R, Sharma A. CYP2C9 Polymorphism and Use of Oral Nonsteroidal Anti-Inflammatory Drugs. US Pharmacist. 2021; 54(3):23–30
6. Practical Cardiology Editorial Staff. Aspirin for G6PD Deficient Patients May Deserve a Second Look. Practical Cardiology. 2020
7. Stingl JC, Welker S, Hartmann G, Damann V, Gerzer R. Where Failure Is Not an Option -Personalized Medicine in Astronauts. PLoS One. 2015; 10(10):e0140764
8. . Table of Pharmacogenomic Biomarkers in Drug Labeling. U.S. Food and Drug Administration; 2021.